PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.12.2001
Applicant's or agent's file reference C1005/7008WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/26020	22/09/2000	23/09/1999

Applicant
CELL SCIENCE THERAPEUTICS

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Sülberg, A Tel.+49 89 2399-7548

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C1005/7008WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/26020	22/09/2000	23/09/1999
International Patent Classification (IPC) or national classification and IPC C12N5/00		
Applicant CELL SCIENCE THERAPEUTICS		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/04/2001	18.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Trommsdorff, M Telephone No. +49 89 2399 7361

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/26020

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-34 as originally filed

Claims, No.:

1-23 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

Sequence listing part of the description, pages:

1, filed with the letter of 26.06.01

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	22, 23: no opinion

2. Citations and explanations
   see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Cited d1ocuments

The following documents (D) are referred to in this communication; the numbering is the same as in the search report and will be adhered to in the rest of the procedure:

D1: BAGLEY J ET AL: 'EXTENDED CULTURE OF MULTIPOTENT HEMATOPOIETIC PROGENITORS WITHOUT CYTOKINE AUGMENTATION IN A NOVEL THREE-DIMENSIONAL DEVICE' EXPERIMENTAL HEMATOLOGY,US,NEW YORK, NY, vol.27, no.3, March 1999 (1999-03), p.496-504, ISSN: 0301-472X

D2: CHENG L ET AL: 'HUMAN MESENCHYMAL STEM CELLS SUPPORT PROLIFERATION AND MULTILINEAGE DIFFERENTIATION OF HUMAN HEMATOPOIETIC STEM CELLS' BLOOD,US,W.B. SAUNDERS, PHILADELPHIA, VA, vol. 92, no. 10, SUPPL. 01, 1998, p.57A ISSN: 0006-4971

D3: WO 99 15629 A (CYTOMATRIX) 1 April 1999 (1999-04-01)

D5: BANU N ET AL: 'Targeted differentiation of CD34+ progenitors in a three-dimensional matrix.' BLOOD, vol. 94, no. 10 SUPPL. 1 PART 2, 15 November 1999 (1999-11-15), p.162b Forty-first Annual Meeting of the American Society of Hematology; New Orleans, Louisiana, USA; December 3-7, 1999 ISSN: 0006-4971

D6: BANU N ET AL: 'Neuronal, mesenchymal and hematopoietic cell derived from CD34-Lin- cell from adult bone marrow.' EXPERIMENTAL HEMATOLOGY (CHARLOTTESVILLE), vol.28, no.7 Supplement 1, July 2000 (2000-07), p.46-7, 29th Annual Meeting of the International Society for Experimental Hematology; Tampa, Florida, USA; July 08-11, 2000 ISSN: 0301-472X

D7: WO 99 64565 A (OSIRIS THERAPEUTICS) 16 December 1999 (1999-12-16)

D8: WO 00 17326 A (MUSC FOUNDATION FOR RESEARCH DEVELOPMENT) 30 March 2000 (2000-03-30)

2. Re Item II
Priority

Since the priority document was not available at the time of examination, the priority could not be checked. Thus, for the time being intermediate documents D5-D8 will not be considered as being part of the prior art as defined in the regulations (Rule 64(1)-(3) PCT). The applicant should however bear in mind that if the priority turned out not to be valid for the subject-matter of all claims, said documents could become prejudicial to the novelty or inventiveness of said claims.

3. Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3.1. The claims are directed to a method for *in vitro* culture of hematopoietic progenitor cells to produce differentiated cells of non-hematopoietic lineage.
D1 describes the use of a three-dimensional, tantalum coated porous biomaterial for long term culture of hematopoietic progenitor cells. The data show that cells can be maintained in a multipotent state over a period of 6 weeks when no cytokines are added. Thus, D1 uses the same growth support as used in the application but solves a different problem as the applicants.
In D2 hematopoietic stem cells are grown on mesenchymal stem cells and shown to differentiate in several cell types such as megakaryocytes, osteoclasts. No differentiated cells of non-hematopoietic lineage are shown.
D3 also describes methods for the culture of hematopoietic cells. Here again, the methods are mainly designed to maintain the cells in a multipotent state.
Since, none of the available prior art documents discloses the method of claim 1, claim 1 and its dependent claims 2-23 are novel (Art. 33(2) PCT).

3.2. Claims 1-23 lack an inventive step for the following reasons:
The problem solved in the application was to establish a method that allows the differentiation of hematopoietic progenitor cells into differentiated cells of non-hematopoietic lineage. Claim 1 recites the technical problem without giving any element of the solution and merely redefines the result to achieve, i.e. to establish the "conditions sufficient to produce differentiated cells of non-hematopoietic lineage". The teaching of D1-D3 shows that methods for *in vitro* culture of hematopoietic progenitor cells are known in the art. If the inventive step consists in establishing the right conditions in order to obtain differentiated cells of non-hematopoietic lineage, said conditions must be defined in the claims.
Hence, since the mere recitation of the problem is not inventive, no inventive step can be seen for the subject-matter of claim 1 and its dependent claims 2-23 (Art. 33(3) PCT) (see also Re Item VIII).

3.3. The subject-matter of claims 1-21 is industrially applicable in the field of

pharmaceutical industry (Art. 33(4) PCT). Claims 22-23 however relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

4. **Re Item VI**
Certain documents cited (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99 64565 A	16 Dec 1999	8 June 1999	8 June 1998
WO 00 17326 A	30 March 2000	21 Sept 1999	21 Sept 1998

5. **Re Item VIII**
Certain observations on the international application

5.1. As mentioned above, claim 1 is unclear for the following reasons:
the subject-matter claimed is defined in terms of the result to achieve, i.e. establishing the "conditions sufficient to produce differentiated cells of non-hematopoietic lineage" but no technical features are given to define said conditions. The essential features necessary for solving the technical problem need to be indicated in the claims (decision of the technical board of appeal T 409/91).
Moreover, the scope of the subject-matter of claim 1 is too broad and not fully supported by the description (Art. 6 PCT). Indeed, the description only teaches the obtention of certain types of cells and not of any non-hematopoietic cell. From the examples given, one cannot automatically make the assumption that any type of cell could be obtained starting from hematopoietic precursor cells.